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BDNF in Huntington's Disease: Role in Pathogenesis and Treatment

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1. Introduction

Huntington's Disease (HD) is a neurodegenerative disorder characterized by motor, cognitive, and psychiatric abnormalities, and is inherited in an autosomal dominant fashion (Borrell-Pages et al., 2006). HD is caused by the CAG trinucleotide repeat expansion in the first exon of the gene encoding huntingtin (htt) (The Huntington's Disease Collaborative Research Group, 1993). This mutation is translated into a polyglutamine (poly Q) stretch near the amino terminus of htt, which results in a toxic gain of function (Gusella & MacDonald, 2000). Although htt is widely expressed in the human body and its mutation is not tissue-specific, the striatum is preferentially affected. The pathological changes in the striatum develop first in the caudate nucleus and then in the putamen, causing a 50-60% neuronal loss in these areas (Mann et al., 1993; Vonsattel & DiFiglia, 1998). Striatal atrophy is due to selective degeneration of medium-sized spiny neurons (MSNs), which comprise 90% of striatal neurons. Interestingly, the MSNs of the indirect pathway, responsible for inhibition of involuntary movement, are preferentially affected, causing motor symptoms of HD such as uncontrollable sequence of movements called "chorea". In the course of the disease, atrophy spreads to other brain regions, including the cerebral cortex, the globus pallidus (GP), and the thalamus (Mann et al., 1993).

The mechanism behind selective degeneration of striatal neurons remains to be elucidated, but it has been suggested that reduced trophic support renders striatal neurons more vulnerable to the toxic actions of mutant htt. Numerous *in vitro* and *in vivo* studies have shown that striatal neurons require brain-derived neurotrophic factor (BDNF) for their survival and function. A deficiency in BDNF-mediated signaling alone is sufficient to cause dendritic abnormalities and neuronal loss in the cerebral cortex and striatum (Baquet et al., 2004; Gorski et al., 2003). Moreover, reduced levels of striatal BDNF were detected in both HD animal models (Apostol et al., 2008; Gharami et al., 2008; Spires et al., 2004) and HD patients (Ferrer et al., 2000). These observations raise the possibility that reduced levels of striatal BDNF may significantly contribute to HD pathogenesis. In support of this view, the progression of HD is accelerated in *Bdnf* heterozygous mice (Canals et al., 2004). Furthermore, alterations of gene expression profile in the striatum have been shown to be similar in HD patients and mice in which the *Bdnf* gene is deleted in the cerebral cortex (Strand et al., 2007). Importantly, the receptor for BDNF, tropomyosin related kinase B (TrkB), is preferentially expressed in striatal MSNs of the indirect pathway, which may explain why this population of neurons is degenerated first in HD patients (Baydyuk et al., 2011).

BDNF found in the striatum is synthesized and anterogradely transported from the cell bodies located in the cerebral cortex, substantia nigra pars compacta, amygdala, and thalamus (Altar et al., 1997; Baquet et al., 2004). Since striatum does not produce BDNF but depends on it for proper function, abnormalities in anterograde transport and reduced gene expression in brain regions supplying BDNF to the striatum might contribute to neuronal dysfunction and death seen in HD (Gauthier et al., 2004; Zuccato et al., 2001). In light of these findings, efforts have been made to test whether increasing BDNF expression represents a valuable strategy for treatment of Huntington's Disease. Indeed, increasing striatal BDNF levels by a transgene, viral delivery, or stimulations that induce *Bdnf* gene expression have been shown to improve disease phenotypes in several HD mouse models (Cho et al., 2007; Gharami et al., 2008; Xie et al., 2010).

This book chapter will review these recent discoveries regarding the role of BDNF deficiency in the pathogenesis of HD and BDNF as a potential therapeutic agent for HD.

2. Wild-type but not mutant htt promotes *Bdnf* gene expression

The pathogenic mechanisms induced by mutant htt are not fully understood but are thought to involve the gain of toxic function and/or the loss of normal activities. Htt is a ubiquitously expressed protein, highly enriched in the brain (DiFiglia et al., 1995). While its exact functions are unknown, htt has been shown to be essential during embryogenesis and possess anti-apoptotic properties during adulthood (Dragatsis et al., 2000; O'Kusky et al., 1999; Rigamonti et al., 2000). Several mechanisms have been proposed for the neurodegenerative effect of the expanded polyQ tract in htt (Rubinsztein, 2002). Discovery of neuronal intranuclear inclusions in HD patients and HD mouse models led to the hypothesis that these protein aggregates might cause neuronal death. However, studies in mice and cultured neurons indicate that the formation of nuclear inclusions does not correlate with neuronal death (Hodgson et al., 1999; Kim et al., 1999; Laforet et al., 2001; Rubinsztein, 2002; Saudou et al., 1998). At present, the molecular basis for the toxic gain of function associated with mutant htt remains unclear.

The loss of a beneficial activity of normal htt has been proposed to contribute to the pathogenesis of HD. Wild type htt is known to regulate transcription of multiple genes, among which the gene encoding BDNF has received special attention (Zuccato et al., 2001). BDNF is a member of the neurotrophin family, which also includes nerve growth factor (NGF), neurotrophin-3 (NT-3) and neurotrophin-4/5 (NT-4/5) (Reichardt, 2006). BDNF has been shown to promote neuronal growth, survival, and differentiation by activating its TrkB receptor tyrosine kinase (Patapoutian & Reichardt, 2001). Upon binding to BDNF, activated full-length TrkB triggers multiple intracellular signaling cascades through protein-protein interactions (Chao, 2003). TrkB-initiated signaling pathways have been shown to promote cell survival by up-regulating the activity of survival genes and inhibiting the function of the proteins that lead to programmed cell death (Bhave et al., 1999; Encinas et al., 1999; Yamada et al., 2001). TrkB signaling pathways can also mediate various synaptic reorganization processes, including formation and maintenance of dendrites and dendritic spines (McAllister et al., 1999). In support of these *in vitro* observations, deletion of either the *TrkB* or *Bdnf* gene leads to cell atrophy, dendritic degeneration, and neuronal loss, as shown in the excitatory neurons of the dorsal forebrain (Gorski et al., 2003; Xu et al., 2000).

In rodents and humans, the *Bdnf* gene is transcribed from at least 8 discrete promoters, producing many different *Bdnf* mRNA species that encode the same protein (Aid et al., 2007). The different transcripts are generated in different tissues in a stimulus- and development-specific manner and may have differential subcellular localizations and targets (Metsis et al., 1993; Pattabiraman et al., 2005; Timmusk et al., 1993). Zuccato et al. have shown that wild-type *htt* enhances *Bdnf* transcription from promoter II, whereas mutant *htt* suppresses *Bdnf* transcription from promoter II as well as two other *Bdnf* promoters in cultured cells and the cerebral cortex of YAC72 transgenic mice expressing mutant *htt* with an expanded tract of 72 glutamines (Zuccato et al., 2001). The same group further investigated the mechanism underlying *Bdnf* gene regulation by wild-type and mutant *htt*, and found that wild-type *htt* promotes transcription of promoter II by sequestering the repressor element-1 transcription factor/neuron restrictive silencer factor (REST/NRSF) in the cytoplasm, thereby freeing the nucleus of the inhibitory complex and allowing transcription to occur (Zuccato et al., 2003). In contrast, mutant *htt* is unable to retain REST/NRSF complex in the cytoplasm, leading to aberrant accumulation of REST/NRSF in the nucleus and inhibition of *Bdnf* gene transcription. Interestingly, the effect of *htt* on *Bdnf* gene expression in cortical neurons is specific since the protein does not affect expression of two other neurotrophins, NGF and NT-3, in cortical neurons (Zuccato et al., 2003). In agreement with these findings, levels of *Bdnf* mRNA are reduced in the cerebral cortices of HD patients (Zuccato et al., 2008). It also has been shown that lower levels of BDNF are associated with higher numbers of CAG repeats in mutant *htt* alleles and correlate with the severity of the disease (Ciammola et al., 2007). It is important to note, however, that this autopsy data should be interpreted with caution. As mutant *htt* alters electrophysiological properties of cortical neurons (Cummings et al., 2009) and neuronal activity regulates *Bdnf* gene expression (Aid et al., 2007), we should not exclude the possibility that the observed reduction in cortical *Bdnf* mRNA levels may be secondary to neurodegeneration.

Although the contribution of suppressed *Bdnf* transcription to reduced BDNF levels in HD striatum is a widely accepted hypothesis, there are studies that contradict this idea. A reduction in *Bdnf* transcription would predict reduced levels of BDNF protein in cerebral cortices of both HD patients and mouse models. This prediction has been confirmed in one study (Zuccato et al., 2008) but not in another study (Gauthier et al., 2004) using post-mortem tissues from multiple control subjects and HD patients. Furthermore, *in situ* hybridization revealed normal levels of cortical *Bdnf* mRNA in aging YAC128 mice that express the whole human *htt* gene with 128 CAG repeats (Xie et al., 2010). Consistent with this observation, levels of cortical BDNF in YAC128 mice and R6/1 mice, another HD model, were found to be similar to those in WT mice (Gharami et al., 2008; Xie et al., 2010). Further analysis of *Bdnf* gene expression in other HD mouse models at various ages is necessary to clear the discrepancy. Despite the discrepancy in determining cortical *Bdnf* mRNA levels, a significant reduction in striatal BDNF has been consistently shown in both HD patients and animal models.

3. Htt promotes axonal BDNF transport

Studies by Gauthier et al. indicate that in addition to controlling *Bdnf* mRNA production in the cortex, wild-type *htt* may also regulate BDNF transport along the corticostriatal axes (Gauthier et al., 2004). The idea that *htt* is involved in intracellular trafficking arose from the subcellular

localization of htt and its association with various proteins of molecular motors. Although present in the nucleus, htt is predominantly found in the cytoplasm, where it interacts with the huntingtin-associated protein-1 (HAP1), a protein involved in axonal transport via association with p150^{glued} subunit of dynactin, which is an essential part of the microtubule-based motor complex (Block-Galarza et al., 1997; Engelender et al., 1997; Li et al., 1998). While htt and other pathogenic polyQ-containing proteins have been shown to affect fast axonal transport (Gunawardena et al., 2003; Szebenyi et al., 2003), the link between deficient trafficking and selective neuronal degeneration has not been established. Gauthier and colleagues show that in normal condition wild-type htt promotes neuronal survival by facilitating the transport of BDNF-containing vesicles along microtubules. Consistent with a loss of function hypothesis, reduction in wild-type htt levels leads to attenuated BDNF trafficking. On the other hand, mutation in htt increases association of polyQ-htt and p150^{glued} via HAP1 and prevents efficient movement of BDNF-containing vesicles along microtubules. They also demonstrate that disruption of BDNF transport leads to decreased neurotrophic support and neurotoxicity, which can be rescued by wild-type htt (Gauthier et al., 2004).

BDNF synthesized in the cortex and transported to the striatum via corticostriatal projections provides the main support for survival of striatal neurons in the adult brain (Altar et al., 1997; Baquet et al., 2004). Importantly, it has been shown that BDNF levels are reduced in the striatum but not in the cortex of HD patients (Gauthier et al., 2004). These observations are in agreement with the notion that both mechanisms, suppressed *Bdnf* gene expression and deficient BDNF transport, might concomitantly contribute to reduced levels of BDNF in the striata of HD patients and mouse models, thus providing strong evidence for BDNF as a crucial factor in the pathogenesis of HD.

4. Possible effects of mutant htt on BDNF maturation

One additional cause for reduced neurotrophic support of striatal neurons in HD may be due to deficits in processing of proBDNF. The proBDNF is a 32-kDa precursor protein that is cleaved to generate the mature BDNF protein of 14 kDa. Whereas the mature form binds to its TrkB receptor and promotes neuronal survival, the uncleaved proBDNF preferentially activates the low-affinity neurotrophin receptor p75NTR (Hempstead 2006), which is a member of the tumor necrosis factor receptor subfamily and is known to induce neuronal death via apoptosis (Frade & Barde, 1998; Teng et al., 2005).

As discussed earlier, immunoblotting analysis has consistently found a reduction in striatal levels of mature BDNF in HD mouse models (Apostol et al., 2008; Gharami et al., 2008; Spires et al., 2004; Xie et al., 2010) and HD patients (Ferrer et al., 2000; Gauthier et al., 2004). However, studies using ELISA assays reported normal striatal levels of BDNF in R6/1 HD mice (Canals et al., 2004; Pang et al., 2006) and increased striatal levels of BDNF in YAC72 mice (Seo et al., 2008). As ELISA assays detect both mature BDNF and proBDNF, this discrepancy suggests that maturation of proBDNF may be impaired in the striatum, leading to accumulation of proBDNF in the striatum. Impaired proBDNF maturation could be detrimental to striatal neurons, because they lose the protective effect of mature BDNF via TrkB receptor signaling and are subject to the apoptotic effect of proBDNF via the p75NTR receptor (Teng et al., 2005). As current BDNF antibodies are still problematic in detecting proBDNF on immunoblots, utilization of tagged *Bdnf* knockin mice (Matsumoto et al., 2008; Yang et al., 2009) will help uncover the effect of mutant htt on BDNF maturation.

A recent study has suggested that proteins involved in proBDNF axonal transport might also play a role in BDNF maturation (Yang et al., 2011). As discussed earlier, htt facilitates axonal transport via its interaction with HAP1 and the mutation in htt alters the formation of proper motor complex and inhibits BDNF transport (Gauthier et al., 2004). Yang et al. found that proBDNF interacts with both HAP1 and sortilin, a binding partner of p75NTR, to form a complex that prevents proBDNF degradation and modulates proBDNF targeting to dendrites and axonal organelles. Furthermore, their data suggest that the complex of proBDNF-HAP1-sortilin might facilitate cleavage and release of mature BDNF (Yang et al., 2011). Thus, it is possible that mutant htt can affect both BDNF maturation and trafficking via its interaction with HAP1.

5. BDNF and selectivity of striatal degeneration

Striatal neurons are not uniformly affected in HD. Immunohistochemical studies using tissues from HD patients have shown a greater decrease in the number of neurons co-expressing the dopamine receptor D2 (Drd2) and enkephalin (Enk) (Reiner et al., 1988). These neurons comprise the indirect pathway, projecting to the external segment of globus pallidus. The indirect pathway acts to terminate basal ganglia associated movements or suppress unwanted sequences of movements (Bolam et al., 2000). Hence, the loss of the indirect pathway neurons leads to disinhibition of the thalamus and increased facilitation of the motor cortex, producing hyperkinesias in HD patients (Calabresi et al., 1996). On the other hand, the direct pathway neurons co-expressing the dopamine receptor D1 (Drd1) and substance P (SP) are less affected in HD. In contrast, striatal interneurons containing acetylcholine, somatostatin/neuropeptide Y, or parvalbumin are spared in patients with HD; a striking phenomenon considering the fact that these cell populations comprise only 5% of striatal neurons (Ferrante et al., 1987a; Ferrante et al., 1987b). These findings suggest that the Drd2/Enk neurons of the striatum may be more vulnerable to the deleterious effects of mutated htt. However, the precise mechanism of this selective neuronal loss is unknown.

Genetic studies using HD mouse models with altered levels of BDNF indicate that BDNF plays an important role in this specificity of degeneration. Depletion of BDNF using heterozygous or forebrain-specific knockout mice results in alterations of striatal gene expression profiling that more closely recapitulates human HD than any other HD models (Strand et al., 2007). Deletion of one copy of the *Bdnf* gene in R6/1 HD mice resulted in early onset of the disease, more severe motor dysfunction, and led to a significant and selective loss of Drd2/Enk striatal neurons (Canals et al., 2004). Data originated in our laboratory show that the loss of striatal neurons was associated with reduced levels of mRNAs for both Enk and Drd2 in YAC128 HD mice (Xie et al., 2010), indicating selective degeneration of striatal neurons in the indirect pathway. Our recent data suggest that selective vulnerability of striatal neurons in the indirect pathway is due to differential expression of the TrkB receptor among striatal neurons. We found that the majority of the TrkB receptor was localized in striatal neurons of the indirect pathway in the adult mouse brain and deletion of TrkB receptor in the developing striatum caused selective loss of this neuronal population (Baydyuk et al., 2011). Together, all these findings indicate that a decrease in striatal BDNF can lead to dysfunction and death of MSNs in the indirect pathway, producing severe motor phenotype as seen in HD. Hence, restoring BDNF levels in the striatum may delay or even stop disease progression.

6. Increasing BDNF expression rescues disease phenotypes in HD mouse models

The evidence discussed above clearly indicates that the reduction in striatal BDNF levels plays a pivotal role in the pathogenesis of HD. Therefore, it is not surprising that efforts have been made to examine whether increasing BDNF expression represents a valuable strategy for treatment of Huntington's Disease. Indeed, increasing striatal BDNF levels via stimulation that induces *Bdnf* gene expression (Duan et al., 2003; Peng et al., 2008; Simmons et al., 2009; Spires et al., 2004) or by viral delivery (Cho et al., 2007) has been shown to improve disease phenotypes in several HD mouse models.

Early symptoms of HD are manifested by cognitive and memory deficits that start before characteristic motor dysfunction (Ho et al., 2003; Lawrence et al., 1998). In HD mouse models, impaired learning and memory, measured as hippocampal long-term potentiation (LTP), occur prior to motor deficits and neuronal loss (Mazarakis et al., 2005; Murphy et al., 2000; Van Raamsdonk et al., 2005). LTP, a form of synaptic plasticity, is potentiated by release of BDNF. Thus, reduced levels of BDNF in HD patients and mice can disrupt synaptic changes important for learning and memory formation. Applying low concentrations of BDNF to hippocampal slices prepared from HD mice fully restores LTP (Lynch et al., 2007). Furthermore, up-regulation of endogenous BDNF levels with an ampakine, a positive modulator of AMPA-type glutamate receptors, rescues synaptic plasticity and reduces learning deficits in HD mice (Simmons et al., 2009).

Altered neurogenesis has been reported in HD mouse models and in human postmortem brains (Curtis et al., 2003; Gil et al., 2005; Phillips et al., 2005). It has been shown that in addition to promoting survival and inducing synaptic plasticity, BDNF also regulates adult neurogenesis (Bath et al., 2011; Henry et al., 2007; Scharfman et al., 2005). The adenoviral delivery of BDNF and Noggin (a known suppressor of gliogenesis) to the striatum of R6/2 HD mice resulted in induction of striatal neurogenesis (Cho et al., 2007). The majority of the newly born neurons differentiated to MSNs and became functional, leading to delayed motor impairment and prolonged survival in R6/2 mice. Similar improvements have been seen in the same HD mouse model after administration of the antidepressant sertraline (Peng et al., 2008). By increasing BDNF levels and stimulating neurogenesis, sertraline treatment resulted in improved motor performance, reduced striatal atrophy, and prolonged survival.

To more directly evaluate the effect of increasing cortical BDNF supply to the striatum on the progression of HD, we overexpressed BDNF in the mouse forebrain by employing a *Bdnf* transgene under the control of the promoter for Ca^{2+} /calmodulin-dependent protein kinase II alpha (Gharami et al., 2008; Xie et al., 2010). This transgene starts to express BDNF in the cerebral cortex in the first postnatal week and reaches plateau in the third postnatal week, as does the endogenous *Bdnf* gene (Huang et al., 1999). It also expresses at low levels in the striatum where the endogenous *Bdnf* gene is mostly inactive (Gharami et al., 2008; Xie et al., 2010). We found that the *Bdnf* transgene was able to greatly increase BDNF levels in the striata of R6/1 and YAC128 mice, indicating that overexpressed BDNF in the cortex is efficiently transported to the striatum despite expression of mutant htt. Importantly, BDNF overexpression reversed brain atrophy, normalized the expression of several important genes in the striatum, and ameliorated deficits in motor coordination in these two HD

mouse models (Gharami et al., 2008; Xie et al., 2010). In addition, overexpression of BDNF in YAC128 mice prevented loss of striatal neurons, normalized spine abnormalities of medium-sized spiny neurons, and significantly improved procedural learning (Xie et al., 2010). In summary, these studies suggest that increasing striatal BDNF supply may have therapeutic potential for HD.

7. Conclusion

Many pathways have been proposed to contribute to the pathogenesis of HD. Recent studies have identified complex molecular mechanisms that mediate neuronal dysfunction and death; these include transcriptional dysregulation, excitotoxicity, impaired axonal transport, and altered synaptic transmission. The findings presented in this chapter support the hypothesis that reduced striatal BDNF plays a crucial role in HD pathogenesis. Currently, drugs used to treat HD act on the symptoms and do not slow or stop the disease progression. Attempting to restore striatal BDNF levels or activate downstream signaling pathways may have therapeutic potential in treating HD patients.

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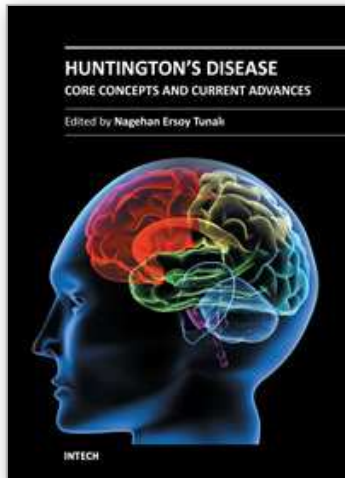
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Huntington's Disease is one of the well-studied neurodegenerative conditions, a quite devastating and currently incurable one. It is a brain disorder that causes certain types of neurons to become damaged, causing various parts of the brain to deteriorate and lose their function. This results in uncontrolled movements, loss of intellectual capabilities and behavioural disturbances. Since the identification of the causative mutation, there have been many significant developments in understanding the cellular and molecular perturbations. This book, "Huntington's Disease - Core Concepts and Current Advances", was prepared to serve as a source of up-to-date information on a wide range of issues involved in Huntington's Disease. It will help the clinicians, health care providers, researchers, graduate students and life science readers to increase their understanding of the clinical correlates, genetic aspects, neuropathological findings, cellular and molecular events and potential therapeutic interventions involved in HD. The book not only serves reviewed fundamental information on the disease but also presents original research in several disciplines, which collectively provide comprehensive description of the key issues in the area.

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